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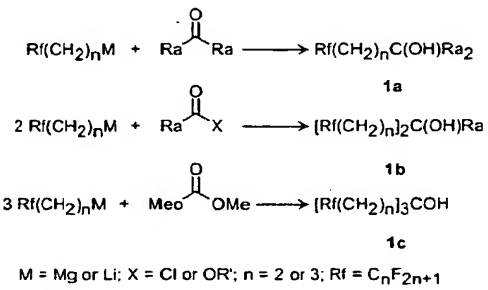
(54) Title: FLUOROUS TAGGING COMPOUNDS AND METHODS OF INCREASING THE FLUOROUS NATURE OF COMPOUNDS

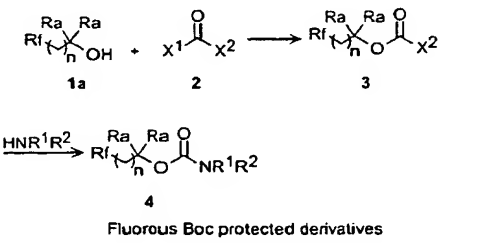
(57) Abstract: A method of increasing the fluorous nature of a compound includes the step of reacting the compound with at least one second compound having formula (I) wherein Rf is a fluorous group, Rs is a spacer group, d is 1 or 0, m is 1, 2 or 3, Ra is an alkyl group and X is a suitable leaving group. A compound has formula (II) wherein Rf is a fluorous group, n is an integer between 0 and 6, m is 1, 2 or 3, Ra is an alkyl group and X is a leaving group.

Preparations of alcohols

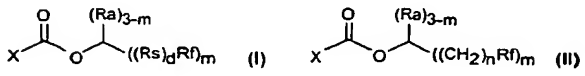


M = Mg or Li; X = Cl or OR'; n = 2 or 3; Rf = C_nF_{2n+1}

Preparations of Boc reagents and reaction with amines



Fluorous Boc protected derivatives



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TITLE

FLUOROUS TAGGING COMPOUNDS AND METHODS OF INCREASING THE FLUOROUS NATURE OF COMPOUNDS

Field of the Invention

The present invention relates to fluorous tagging compounds and to methods of increasing the fluorous nature of compounds.

Background of the Invention

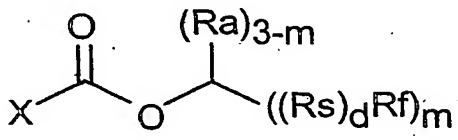
Organic chemists are typically trained that organic compounds have to be synthesized as pure substances through well-planned reactions and scrupulous separation. In fields such as drug discovery, catalyst design and new material development, however, tens of thousands of organic compounds must be synthesized and tested to discover a few active ones. In the pharmaceutical industry, for example, synthesizing such a large number of compounds in the traditional way is too slow compared to the rapid emergence of new biological targets. A major factor limiting the productivity of orthodox solution (liquid) phase organic synthesis is the tedious separation process for the purification of products. High throughput organic synthesis, therefore, preferably integrates organic reactions with rapid purification/separation procedures.

Recently, fluorous synthetic and separation techniques have attracted the interest of organic chemists. In fluorous synthetic techniques, reaction components are typically attached to fluorous groups such as perfluoroalkyl groups to facilitate the separation of products. In general, fluorous-tagged molecules partition preferentially into a fluorous phase while non-tagged ones partition into an organic phase. Although fluorous synthetic and/or separation techniques are promising, such techniques are currently limited by a lack of availability of suitable fluorous tags.

It is thus very desirable to develop fluorous tagging compounds and methods of increasing the fluorous nature of compounds.

Summary of the Invention

In one aspect, the present invention provides a method of increasing the fluorous nature of a compound. The method includes the step of reacting the compound with at least one second compound having the formula:



wherein Rf is a fluorous group (for example, a fluoroalkyl group, a fluorinated ether or another highly fluorinated

group), Rs is a spacer group, d is 1 or 0 (that is, Rs may be present or absent), m is 1, 2 or 3, Ra is an alkyl group and X is a suitable leaving group. Suitable leaving groups include, but are not limited to, a halide (F, Cl, Br or I), $-N_3$, CN, RO-, NH_2O-, NHRO-, NR_2O-, RCO_2-, $ROCO_2$-, $RNCO_2$-, RS-, RC(S)O-, RCS_2-, RSC(O)S-, $RSCS_2$- $RSCO_2$-, ROC(S)O-, $ROCS_2$-, RSO_2-, RSO_3-, $ROSO_2$-, $ROSO_3$-, RPO_3-, $ROPO_3$-, an N-imidazolyl group, an N-triazolyl group, an N-benzotriazolyl group, a benzotriazolyloxy group, an imidazolyloxy group, an N-imidazolinone group, an N-imidazolone group, an N-imidazolinethione group, an N-imidazolinthione group, an N-succinimidyl group, an N-phthalimidyl group, an N-succinimidyloxy group, an N-phthalimidyloxy group, -ON=C(CN)R, or a 2-pyridyloxy group. R is preferably an alkyl group or an aryl group.

The terms "alkyl", "aryl" and other groups refer generally to both unsubstituted and substituted groups unless specified to the contrary. Unless otherwise specified, alkyl groups are hydrocarbon groups and are preferably C_1-C_{15} (that is, having 1 to 15 carbon atoms) alkyl groups, and more preferably C_1-C_{10} alkyl groups, and can be branched or unbranched, acyclic or cyclic. The above definition of an alkyl group and other definitions apply also when the group is a substituent on another group. The term "aryl" refers to phenyl (Ph) or napthyl, substituted or unsubstituted. The terms "alkylene" refers to bivalent forms of alkyl.

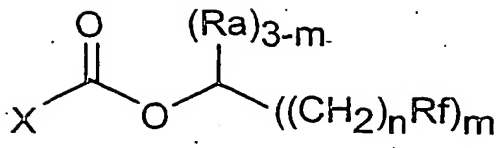
The groups set forth above, can be substituted with a wide variety of substituents. For example, alkyl

groups may preferably be substituted with a group or groups including, but not limited to, halide(s). Preferably, halide constituents are F and/or Cl. Aryl groups may preferably be substituted with a group or groups including, but not limited to, halide(s), alkyl group(s), a cyano group(s) and nitro group(s). As used herein, the terms "halide" or "halo" refer to fluoro, chloro, bromo and iodo. Preferred halide substituents are F and Cl.

The resulting fluorous "tagged" compound can be used in a variety of fluorous reaction and/or separation techniques. Such fluorous reaction and separation techniques are disclosed, for example, in U.S. Patent Nos. 5,859,247 and 5,777,121 and U.S. Patent Application Serial No. 09/506,779, assigned to the assignee of the present invention, the disclosures of which are incorporated herein by reference.

Preferably, the molecular weight of the fluorous tag of the present invention does not exceed about 2,500. More preferably, the molecular weight does not exceed about 2,000. Even more preferably the molecular weight does not exceed about 1,750. Compounds may bear more than one fluorous tag of the present invention.

In another aspect, the present invention provides a compound (a fluorous tagging compound) having the formula:



wherein Rf is a fluorous group (for example, a fluoroalkyl group, a fluorinated ether or another highly fluorinated group), n is an integer between 0 and 6, m is 1, 2 or 3, Ra is an alkyl group and X is a leaving group. Ra is preferably C_1-C_6 alkyl group.

As used herein, the term "fluorous", when used in connection with an organic (carbon-containing) molecule, moiety or group, refers generally to an organic molecule, moiety or group having a domain or a portion thereof rich in carbon-fluorine bonds (for example, fluorocarbons or perfluorocarbons, fluorohydrocarbons, fluorinated ethers and fluorinated amines). The term "fluorous compound," thus refers generally to a compound comprising a portion rich in carbon-fluorine bonds. As used herein, the term "perfluorocarbons" refers generally to organic compounds in which all hydrogen atoms bonded to carbon atoms have been replaced by fluorine atoms. The terms "fluorohydrocarbons" and "hydrofluorocarbons" include organic compounds in which at least one hydrogen atom bonded to a carbon atom has been replaced by a fluorine atom. A few examples of suitable fluorous groups Rf for use in the present invention include, but are not limited to, $-C_4F_9$, $-C_6F_{13}$, $-C_8F_{17}$, $-C_{10},F_{21}$, $-C(CF_3)_2C_3F_7$, $-C_4F_8CF(CF_3)_2$, and $-CF_2CF_2OCF_2CF_2OCF_3$.

As used herein, the term "tagging" refers generally to attaching a fluorous moiety or group (referred

to as a "fluorous tagging moiety" or "tagging group") to a compound to create a "fluorous tagged compound". Separation of the tagged compounds of the present invention is achieved by using fluorous separation techniques that are based upon differences between/among the fluorous nature of a mixture of compounds. As used herein, the term "fluorous separation technique" refers generally to a method that is used to separate mixtures containing fluorous molecules or organic molecules bearing fluorous domains or tags from each other and/or from non-fluorous compounds based predominantly on differences in the fluorous nature of molecules (for example, size and/or structure of a fluorous molecule or domain or the absence thereof). Fluorous separation techniques include but are not limited chromatography over solid fluorous phases such as fluorocarbon bonded phases or fluorinated polymers. See, for example, Danielson, N.D. et al., "Fluoropolymers and Fluorocarbon Bonded Phases as Column Packings for Liquid Chromatography," J. Chromat., 544, 187-199 (1991). Examples of suitable fluorocarbon bonded phases include commercial Fluofix® and Fluophase™ columns available from Keystone Scientific, Inc. (Bellefonte, PA), and FluoroSep™-RP-Octyl from ES Industries (Berlin, NJ). Other fluorous separation techniques include liquid-liquid based separation methods such as liquid-liquid extraction or countercurrent distribution with a fluorous solvent and an organic solvent.

Brief Description of the Drawings

Figure 1 illustrates synthesis and introduction of fluorous BOC groups.

Figure 2 illustrates synthesis of a fluorous BOC reagent of the present invention and its attachment to an amine and detachment from the resulting amide.

Figure 3 illustrates recovery of a fluorous BOC compound of the present invention.

Figure 4 illustrates the utility of fluorous BOC compounds of the present invention in separating a library of compounds.

Figure 5 illustrates the structure of several amides generated from fluorous BOC tagging compounds of the present invention.

Figure 6 illustrates several products generated by deprotection of fluorous BOC protected amines.

Figure 7 illustrates fluorous BOC groups with different fluorine content and spacer groups.

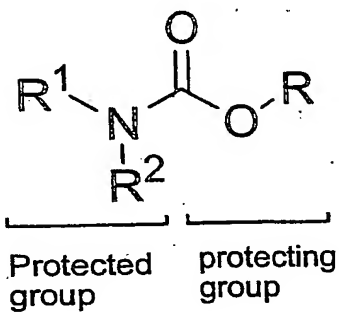
Figure 8 illustrates the synthesis of the 96-compound library that is described in Example 15.

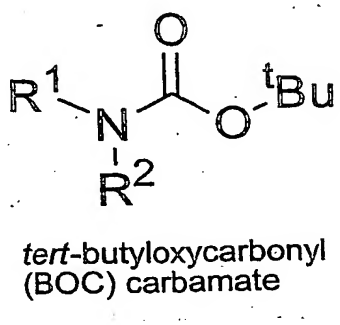
Figure 9 illustrates the isolated yields of the 96-compound library of Figure 8.

Detailed Description of the Invention

Carbamates are an important class of protecting group for nitrogen. For example, virtually all peptide synthesis schemes rely on carbamate protecting groups of some sort, and carbamates are commonly used in alkaloid synthesis and other areas. One of the most useful carbamates is the tert-butyloxycarbonyl group (commonly referred to as the "BOC" group) illustrated below:

A carbamate





In the present invention, a new class of fluorous carbamates referred to herein as fluorous BOC compounds or groups were synthesized after the BOC group. The fluorous tagging groups of the present invention can, for example, be reacted with nitrogen-bearing groups such as amine groups ($-NR^1R^2$) of compounds to create a fluorous-tagged (or protected) compound.

The fluorous BOC (^{F}BOC) groups of the present invention generally act like traditional BOC and other carbamate groups to protect nitrogen-based functional groups during organic reactions. Protecting groups are discussed generally in Greene, T. W.; Wuts, P. G. M. Protective Groups in Organic Synthesis; 3rd ed.; Wiley-Interscience: New York, (1999) and Kocienski, P. "Protecting groups", Thieme: Stuttgart (1994). However, the fluorous BOC groups of the present invention have advantages over other traditional carbamate and other protecting groups in that they facilitate separation of the ^{F}BOC-protected (fluorous-tagged) products from each other and from non-tagged reaction components. Additionally, the fluorous domain of the fluorous BOC groups are useful not only for attachment to nitrogen, but also to oxygen, sulfur and other heteroatoms. The resulting ^{F}BOC carbonates, thiocarbamates, etc. serve substantially the same purpose and are used analogously to the ^{F}BOC carbamates described in greater detail herein.

The reagents used for the protection of amines with fluorous BOC groups are generally prepared as shown in Figure 1. Fluorous alcohols **1a-c** bearing one, two or three fluorous chains are readily synthesized, for example, by nucleophilic addition reactions. Addition of an organometallic reagent $Rf(CH_2)_nM$ (wherein, M is, for example, lithium, magnesium halide, etc. and Rf is a fluorous group) to an appropriate ketone generates an alcohol **1a** with one fluorous chain and two alkyl groups. Similarly, alcohols with two fluorous chains **1b** can be generated by organometallic addition to esters, acids

chlorides or related molecules, and alcohols with three fluorous chains **1c** can be generated by nucleophilic additions to carbonate esters, phosgene, or related molecules. The alcohols with two and three fluorous chains prepared by these routes usually contain the same fluorous group, but alcohols with different fluorous groups can be prepared by several routes. For example, addition of $Rf^1(CH_2)_{n1}M$ to an aldehyde followed by oxidation of the resulting secondary alcohol and addition of $Rf^2(CH_2)_{n2}M$ results in an alcohol with two different fluorous chains (Rf^1 and Rf^2) spaced by alkylene spacers that can be the same or different. A series of fluorous alcohols with different numbers of fluorines is useful, for example, in fluorous mixture synthesis techniques. See, U.S Patent Application Serial No.09/506,779.

Fluorous BOC reagents **3** can be prepared by one of many schemes known to those skilled in the art for the conversion of standard alcohols to activated carbamoylating agents. For example, alcohols bearing one fluorous chain and two alkyl groups can react with one of many reagents **2**, which can be considered as doubly activated derivatives of carbonic acids. In Figure 1, the leaving group (X) is a part of the molecule that is cleaved in the substitution reaction. Many different leaving groups suitable for use in the present invention are known to those skilled in the art. For the purposes of this invention, leaving groups whose conjugate acids have a pKa of less than about 18 are preferred. Leaving groups whose conjugate acids have a pKa of less than about 10 are more preferred. Even more preferred are leaving groups whose conjugate acids have a

pKa of less than about 5. In a preferred method, the fluorous alcohol **1a** is first reacted with the reagent **2** to displace the first leaving group to give **3**. The intermediate BOC reagent **3** may be isolated prior to reaction with an amine under standard conditions, or it may be reacted directly with the amine *in situ* without isolation. Either or both of the acylation reactions may be catalyzed by standard catalysts known to those skilled in the art. An example on one such acylation catalyst is 4-dimethylaminopyridine (DMAP). Fluorous BOC reagents with two or three fluorous chains are prepared and reacted analogously to those with one chain.

Reactions and Compounds in the Examples:

The synthesis of a representative fluorous BOC (^{F}BOC) reagent **7** of the present invention and its attachment to a typical amine **8** and detachment from the resulting amide **9** are shown in Figure 2. Reaction of perfluorooctylethyl iodide with t-BuLi followed by addition of acetone and workup and chromatographic purification provided the alcohol **5** in 60% yield. Activated reagent **6** was generated according to the literature methods set forth in M. Itoh, et. al, *Bull. Chem. Soc. Jpn.*, *50*, 718 (1977), and then reacted with alcohol **5**. Workup and chromatography provided the representative ^{F}BOC reagent **7** as a solid. Protection of amino amide **8** with the ^{F}BOC reagent **7** was accomplished under standard conditions and gave ^{F}BOC derivative **9** in quantitative yield. ^{F}BOC-protected **9** could be deprotected to regenerate **8** by treatment with neat TFA for 40 min followed by evaporation and vacuum drying to

remove the fluorous BOC remnants and other volatile compounds. The fluorous BOC remnants can also be removed by solid phase extraction over fluorous reverse phase silica gel.

The ability to recover the fluorous BOC component for reuse is demonstrated by the results of Figure 3. Coupling of **7** with dimethyl amine provided **10** in 95% yield. Cleavage of **10** with 30/70 CH_2Cl_2/TFA followed by evaporation provided the trifluoroacetate **11** in 100% yield. Trifluoroacetate **11** was hydrolyzed by treatment with lithium hydroxide in methanol to provide the starting alcohol **5** in 87% yield.

To demonstrate the utility of the fluorous BOC group in facilitating reaction separation, a 16 compound library of amides was made by parallel synthesis as shown in Figure 4. Amines **12a-d** were reacted with the ^{F}BOC reagent **7** as in Figure 2 to give ^{F}BOC protected acids **13a-d**. Each of the four acids was coupled with amines **14a'-d'** under standard amide formation conditions using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDI), *N*-hydroxybenzotriazole (HOBt), and triethylamine (Et_3N). These reaction mixtures were purified by solid phase extraction using a commercially available semi-preparative Fluofix column. The fluorous tagged products are readily separated from all non-tagged reaction components. Yields and structures for the coupled products **15aa'-dd'** are illustrated in Figure 5.

To demonstrate the removal of the fluorous BOC group, four of the products were heated in 3N HCl/MeOH at 60°C for 16 h. All the volatile products (including the residual fluorous products) were removed by exposure to high vacuum, and then the yields of the final amine hydrochlorides were determined by NMR analysis as described in the Examples. These products are shown in Figure 6. A second library of eight amines involving the steps of ^{F}BOC protection, amide formation with rapid purification by fluorous solid phase extraction, and removal of the ^{F}BOC group with TFA, is also described in Example 15. The resulting secondary amines were used to make 96 tertiary amines.

The amides shown in Figure 7 were prepared to demonstrate that other fluorous BOC groups with different numbers of fluorous chains and different spacer elements could also be used. The syntheses of the respective ^{F}BOC precursors and the amides themselves are described in the Examples. The retention times of amides **16a-c** were then measured on an analytical Fluofix column, eluting with the gradient shown in Figure 7. The retention times of these amides are all longer than that of amide **9**. This is expected because they have more fluorines. Under these conditions, most non-fluorous tagged organic compounds have retention times at or near the solvent front (approximately 2-3 minutes). Since **9** can be separated by fluorous solid phase extraction, it follows that the more strongly retained amides **16a-c** will also be separable from non-tagged compounds by solid phase extraction.

Experimental Examples

Example 1: Authentic Sample of (3,4-Dihydro-1*H*-isoquinolin-2-yl)piperidin-4-yl-methanone (8). *N*-Trifluoroacetyl isonipecotic acid (2.56 g, 11.4 mmol), tetrahydroisoquinoline (1.82 g, 13.7 mmol), EDCI (2.63 g, 13.7 mmol), HOBT (1.85 g, 13.7 mmol) and triethylamine (1.38 g, 13.7 mmol) were stirred in dry dichloromethane (30 mL) at 25 °C for 6 h. The reaction was quenched with water and the aqueous phase was extracted with dichloromethane. The combined organic phase was dried over $MgSO_4$ and purified by column chromatography (40/60 EtOAc/hexanes). The solid obtained was stirred with excess K_2CO_3 in MeOH at 25 °C overnight (16 h). After evaporation of MeOH, the residue was partitioned between dichloromethane and basic water. Evaporation of the organic phase gave pure product as a colorless solid (2.12 g, 76% for two steps). ^1H NMR ($CDCl_3$) (mixture of two rotamers) δ 7.23 – 7.16 (m, 4H), 4.73 (s, 1H), 4.67 (s, 1H), 3.83 (t, J = 5.9 Hz, 1H), 3.74 (t, J = 5.8 Hz, 1H), 3.21 – 3.16 (m, 2H), 2.92 (t, J = 5.7 Hz, 1H), 2.85 (t, J = 5.7 Hz, 1H), 2.76 – 2.67 (m, 3H), 2.29 (s, 1H), 1.80 – 1.73 (m, 4H); ^{13}C NMR (CD_3OD-$CDCl_3$) δ 175.5, 175.3, 135.8, 135.1, 134.0, 133.8, 129.6, 129.3, 127.9, 127.6, 127.4, 127.3, 127.0, 48.2, 45.8, 45.4, 44.2, 41.4, 40.2, 39.6, 39.5, 30.5, 29.5, 29.4, 29.1; LRMS: m/z (relative intensity), 244 (M^+, 37%), 188 (100%), 132 (74%); HRMS: calcd. for $C_{15}H_{19}N_2O$ 244.1576, found 244.1574. MP: 75 – 76 °C.

Example 2: 1,5-Bis(perfluorohexyl)-3-methylpentan-3-ol. A portion of 2-perfluorohexylethyl iodide (1.0 mL) was added to a suspension of Mg powder (0.85 g, 35.0 mmol) in dry diethyl ether (5 mL) under argon. The mixture was sonicated for 30 min. To the resulting suspension, a solution of 2-perfluorohexylethyl iodide (total 7.8 ml, 31.8 mmol) in dry diethyl ether (40 mL) was added over 40 – 60 min. Upon completion of addition, the dark mixture was stirred at reflux for 1 h. After cooling down to room temperature, a solution of ethyl acetate (0.9 mL, 11.1 mmol) in diethyl ether (4.0 mL) was added slowly. The mixture was stirred at room temperature overnight before quenching with saturated aqueous NH_4Cl. The aqueous phase was extracted with diethyl ether (3× 20 mL). The ether phase was combined and dried over $MgSO_4$. After evaporation of solvent, the residue was purified by column chromatography with 5:95 ethyl acetate-hexane. The title compound obtained was further recrystallized twice from chloroform to give colorless needles (5.18 g, 79%). ^1H NMR ($CDCl_3$) δ 2.34 – 2.10 (m, 4H), 1.89 – 1.68 (m, 4H), 1.28 (s, 3H), 1.17 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 70.5, 32.0, 26.2, 25.7 (t); IR (Nujol) 3467, 2923, 1461, 1369, 1244, 1140, 1051, 701, 521 cm^{-1}; LRMS *m/z*: 1491 (50%), 1145 (5%), 723 (42%), 375 (100%); HRMS found: C, 29.04%, H, 1.62%. Calcd.: C, 29.28%, 1.64%. MP: 57 – 58 °C.

Example 3: O-Bis(perfluorohexylethyl)ethyloxycarbonyloxyiminophenylaceto nitrile. To a sample tube sealed under argon was charged with a solution of phosgene in toluene (0.27 mL, 0.55 mmol) and the solution was cooled to 0 °C. A solution of 2-hydroxyimino-2-phenylacetonitrile (75 mg, 0.51 mmol) and

dimethylaniline (70 uL, 0.55 mmol) in THF (0.2 mL) and benzene (0.2 mL) was added dropwise to the ice-cooled solution. The mixture was stirred at 0 °C for 6 h. The mixture was placed in a freezer (−20 °C) overnight before returning to the ice bath. A solution of the alcohol from Example 2 (0.39 g, 0.55 mmol) and pyridine (45 uL, 0.55 mmol) in THF (3.0 mL) was added dropwise. The orange mixture was stirred at 0 °C for 6 h and allowed to warm to room temperature over night. The suspension was quenched with water and extracted with diethyl ether. The organic phase was dried over $MgSO_4$. After removal of solvent, the residue was purified by column chromatography with 5:95 ethyl acetate-hexanes to give pure product as a white gum (223 mg, 49%). ^1H NMR ($CDCl_3$) δ 7.95 (d, J = 7.5 Hz, 2H), 7.61 (t, J = 7.3 Hz, 1H), 7.51 (t, J = 7.7 Hz, 2H), 2.42 – 2.08 (m, 8H), 1.66 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 149.7, 138.7, 133.3, 129.4, 127.6, 108.2, 86.1, 28.8, 25.6 (t), 22.8; IR (thin film): 1795, 1450, 1240, 1023, 940, 729 cm^{-1}; FABMS m/z: 910 (M^+, absent), 867 ($M^+ - CO_2$, 21%), 721 (100%), 681 (16%).

Example 4: 1,7-Bis(perfluorobutyl)-4-methylheptan-4-ol. To a solution of 3-perfluorobutylpropyl iodide (688 mg, 1.77 mmol) in a mixture of dry diethyl ether and dry hexane (25 mL, 1:1 v/v) was added ^{t}BuLi (2.2 mL, 1.7 M in pentane, 3.74 mmol) at −78 °C. The mixture was stirred for 1 h during which time the temperature increased to −35 °C. After cooling to −78 °C, acetyl chloride (57 uL, 0.80 mmol) was added dropwise. The cooling bath was removed and the reaction mixture was stirred for 1 h. Water was added to

quench the reaction. After extraction with ether, the organic phase was dried over $MgSO_4$ and evaporated to dryness. The crude product was purified by column chromatography with 5:95 ethyl acetate-hexane to give the alcohol as a yellow oil (103 mg, 23%). ^1H NMR ($CDCl_3$) δ 2.19 - 2.01 (m, 4H), 1.76 - 1.68 (m, 4H), 1.67 - 1.53 (m, 4H), 1.24 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 121.8 - 110.8 (m), 72.4, 41.4, 31.3, 26.7, 15.1; LRMS m/z (relative intensity) 551 (M^+ - Me, 15%), 305 (100%); HRMS found: 551.0676, calcd. for $C_{15}H_{13}F_{18}O$: 551.0679; IR (thin film): 3147, 2975, 1468, 1356, 1206, 880, 720 cm^{-1}.

Example 5: 1,7-Bis(perfluorohexyl)-4-methylheptan-4-ol. This compound was prepared by the same procedure as Example 4 but ethyl acetate was used instead of acetyl chloride. Yield: 68% (white solid). ^1H NMR ($CDCl_3$) δ 2.13 - 2.04 (m, 4H), 1.76 - 1.66 (m, 4H), 1.64 - 1.53 (m, 4H), 1.24 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 122.0 - 107.0 (m), 72.4, 41.4, 31.4 (t), 26.5, 15.1; ^{19}F NMR ($CDCl_3$) δ −81.2 (3F), −114.8 (2F), −122.4 (2F), −123.4 (2F), −124.1 (2F), −126.6 (2F); LRMS: m/z (relative intensity) 751 (M^+ - Me, 77%), 709 (24%), 405 (100%); HRMS found: 751.0570, calcd. for $C_{19}H_{13}OF_{26}$: 751.0566; MP: 46 - 47 °C.

Example 6: 4-Perfluorooctyl-2-methylbutan-2-ol (5). This compound was prepared by the same procedure as Example 4 but acetone was used instead of acetyl chloride. Yield: 60% (white solid). ^1H NMR ($CDCl_3$) δ 2.32 - 2.14 (m, 2H), 1.78 - 1.73 (m, 2H), 1.29 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 122.4 - 107.4 (m), 69.9, 33.5, 29.4, 26.2 (t); LRMS m/z (relative

intensity) 505 (M^+ – H, 12%), 491 (M^+ – Me, 100%); HRMS found: 491.0306; calcd. for $C_{12}H_8F_{17}O$: 491.0304. MP: 50 – 51 °C.

Example 7: O-Bis(perfluorobutylpropyl)ethoxycarbonyloxyiminophenylacetonitrile. This compound was prepared by the same procedure as Example 3. Yield: 27% (gum). ^1H NMR ($CDCl_3$) δ 7.95 (d, J = 8.1 Hz, 2H), 7.60 (t, J = 7.2 Hz, 1H), 7.51 (t, J = 7.5 Hz, 2H), 2.20 – 1.91 (m, 8H), 1.79 – 1.71 (m, 4H), 1.62 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 150.0, 138.3, 133.2, 129.4, 127.6, 121.5 – 114.8 (m), 108.4, 88.7, 37.5, 30.8 (t), 23.1, 14.8; LRMS m/z (relative intensity) 761 (M^+ + Na), 548 (45%), 305 (100%), 287 (90%). IR (thin film): 2982, 1795, 1234, 1132, 1022, 878 cm^{-1}.

Example 8a: O-(Perfluorooctylethyl)isopropanoxycarbonyloxyiminophenylacetonitrile (7). This compound was prepared by the same procedure as Example 3. Yield: 61% (orange solid). ^1H NMR ($CDCl_3$) δ 7.95 (d, J = 8.1 Hz, 2H), 7.60 (t, J = 6.9 Hz, 1H), 7.51 (t, J = 7.8 Hz, 2H), 2.29 – 2.15 (m, 4H), 1.66 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 150.0, 138.3, 133.3, 129.5, 127.9, 127.7, 111.0, 85.9, 31.5, 25.7; ^{19}F NMR ($CDCl_3$) δ –79.6 (3F), –113.2 (2F), –120.7 (6F), –121.5 (2F), –121.9 (2F), –124.9 (2F); LRMS: 634 (16%), 615 (10%), 489 (100%); MP: 76 – 78 °C.

Example 8b. 4-(3,4-Dihydro-1H-isoquinoline-2-carbonyl)-piperidine-1-carboxylic acid

4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoro-1,1,-dimethyl-undecyl ester.

A solution of compound **7** (89 mg, 0.13 mmol) and compound **8** (29 mg, 0.12 mmol) in dichloromethane (4 ml) was stirred at room temperature for 2 h. The mixture was evaporated to dryness. The residue was purified by column chromatography (3:1 EtOAc/hexanes) to give compound **9** (93 mg, 100%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.22 – 7.14 (m, 4H), 4.74 (s, 1H), 4.68 (s, 1H), 4.23 – 4.07 (br, 2H), 3.8 (br, 1H), 3.74 (t, *J* = 2.9 Hz, 1H), 2.96 – 2.74 (m, 5H), 2.22 – 2.01 (m, 4H), 1.74 (br, 4H), 1.51 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 173.4, 173.2, 154.2, 135.3, 133.9, 133.6, 132.6, 129.3, 128.5, 127.3, 126.9, 126.8, 126.6, 126.1, 47.5, 44.7, 43.8, 43.3, 40.2, 39.1, 38.9, 32.1, 30.0, 28.5, 26.2; LRMS: 776 (M^+, 15%) 757 (27%), 739 (22%), 243 (100%), 188 (60%), 132 (45%); HRMS: calcd. for $C_{29}H_{29}N_2O_3F_{17}$: 776.1907, found 776.1894. MP: 114 – 116 °C.

Example 9: 4-(3,4-Dihydro-1*H*-isoquinoline-2-carbonyl)piperidine-1-carboxylic acid 1-perfluorooctylethylisopropyl ester (16a). The fluorous Boc reagent from Example 3 (89 mg, 0.13 mmol), the compound in Example 1 (29 mg, 0.12 mmol) and triethylamine (20 mg, 20.0 mmol) were mixed in dry dichloromethane (4.0 mL) and stirred at room temperature for 2 h. After evaporation of solvent, the residue was purified by column chromatography with 30:70 ethyl acetate-hexane to give pure product as a white solid. Yield: 93 mg (96%); Rf = 0.22 (30:70 ethyl acetate-hexane); ^{1}H NMR (mixture of two rotamers) ($CDCl_3$) δ 7.22 – 7.14 (m, 4H), 4.74 (s, 1H), 4.68 (s, 1H), 4.23 –

4.07 (br, 2H), 3.85 (br, 1H), 3.74 (t, J = 5.8 Hz, 1H), 2.95 - 2.74 (m, 5H), 2.22 - 2.05 (m, 4H), 1.74 (br, 4H), 1.52 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 173.4, 173.2, 154.2, 135.3, 134.0, 133.6, 132.6, 129.3, 128.5, 127.3, 126.9, 126.8, 126.6, 126.1, 122.8 - 107.3 (m), 79.9, 47.5, 44.7, 43.8, 43.3, 40.2, 39.1, 38.9, 32.1, 30.0, 28.5, 26.2; LRMS: m/z (relative intensity) 776 (M^+, 14%), 757 (M^+ - F, 25%), 739 (M^+ - 2F, 20%), 489 (11%), 287 (20%), 271(24%), 243 (100%), 188 (60%), 132 (45%); HRMS calcd. for $C_{29}H_{29}N_2O_3F_{17}$: 776.1907, found: 776.1894; MP: 115 °C.

Example 10: Compound 16b. This compound was prepared by the same procedure as Example 9 with the fluorous Boc reagent from Example 8. Yield: 79% (yellowish oil); ^1H NMR ($CDCl_3$) δ 7.22 - 7.14 (m, 4H), 4.74 (s, 1H), 4.68 (s, 1H), 4.16 (br, 2H), 3.85 (br, 1H), 3.74 (t, J = 5.8 Hz, 1H), 2.95 - 2.74 (m, 5H), 2.18 - 2.00 (m, 6H), 1.75 - 1.60 (m, 10 H), 1.46 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 173.4, 173.2, 154.2, 135.3, 134.0, 133.7, 132.7, 129.5, 129.0, 128.7, 128.2, 127.5, 127.0, 126.7, 126.3, 125.0, 123.3 - 108.7 (m), 82.7, 47.6, 44.7, 43.3, 40.2, 39.0, 38.7, 38.3, 37.9, 31.4, 30.8, 30.3, 30.0, 28.5 (t), 24.6, 23.7, 14.9 (t); LRMS: m/z (relative intensity) 835 (M^+ - H, 35%), 817 (M^+ - F, 23%), 548 (17%), 287 (77%), 243 (100%), 188 (72%), 132 (71%).

Example 11: Compound 16c. This compound was prepared by the same procedure as Example 9 with the fluorous Boc reagent from Example 7. Yield: 100% (white solid); ^1H NMR ($CDCl_3$) δ 7.22 - 7.14 (m, 4H), 4.74 (s, 1H), 4.68 (s, 1H), 4.23 - 4.07 (br, 2H), 3.8 (br, 1H), 3.74 (t, J = 2.9 Hz,

1H), 2.96 – 2.74 (m, 5H), 2.22 – 2.01 (m, 4H), 1.74 (br, 4H), 1.51 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 173.4, 173.2, 154.2, 135.3, 133.9, 133.6, 132.6, 129.3, 128.5, 127.3, 126.9, 126.8, 126.6, 126.1, 47.5, 44.7, 43.8, 43.3, 40.2, 39.1, 38.9, 32.1, 30.0, 28.5, 26.2; LRMS: 776 (M^+, 15%) 757 (27%), 739 (22%), 243 (100%), 188 (60%), 132 (45%); HRMS: calcd. for $C_{29}H_{29}N_2O_3F_{17}$: 776.1907, found 776.1894. MP: 114 – 116 °C.

Example 12: Dimethyl-carbamic acid 4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoro-1,1-dimethylundecyl ester (10). Dimethylamine (300 uL, 2.0 M in THF, 0.60 mmol) was added to a solution of fluorous Boc reagent **7** (101 mg, 0.15 mmol) in THF. The mixture was stirred at room temperature for 1.5 h. After evaporation of solvent, the residue was purified by column chromatography with 10:90 ethyl acetate/hexane (Rf = 0.18) to give pure product (82 mg, 95%); ^1H NMR ($CDCl_3$) δ 2.87 (s, 6H), 2.24 – 1.99 (m, 4H), 1.51 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 155.5, 122.0 – 105.2 (m), 79.4, 35.9, 32.1, 26.0; LRMS: 577 (M^+, 9%), 558 (M^+ – F, 12%), 489 (45%), 90 (70%), 72 (100%); IR (thin film): 2942, 1707, 1454, 1389, 1236, 656 cm^{-1}.

Example 13: Trifluoro-acetic acid 4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoro-1,1-dimethylundecyl ester (11). Dimethylamine (2-perfluorooctylethyl)isopropyl carbamate **10** (251 mg, 0.44 mmol) was stirred with 1:1 CH_2Cl_2/TFA at room temperature overnight. After evaporation of solvent, the residue was partitioned between dichloromethane and aqueous K_2CO_3. The organic phase was dried over $MgSO_4$ and evaporated to give

pure product (262 mg, 100%); ^{1}H NMR ($CDCl_3$)δ 2.22 - 2.08 (m, 4H), 1.63 (s, 6H); ^{19}F NMR ($CDCl_3$) δ −74.6 (3F), −79.6 (2F), −113.3 (2F), −120.8 (6F), −121.6 (2F), −122.1 (2F), −125.0 (2F); ^{13}C NMR ($CDCl_3$) δ 156.4 (t), 121.5 - 105.1 (m), 86.7, 31.5, 25.7 (t), 25.0; LRMS: m/z (relative intensity) 587 (M^+ − Me, 70%), 489 (M^+ − CF_3CO_2, 68%), 155 (82%); HRMS calcd. for $C_{13}H_{10}F_{17}$: 489.0511, found: 489.0504,; IR (thin film): 2992, 1784, 1371, 1214 cm^{-1}.

Example 14: Synthesis of the Library in Figures 4 and 5.

1. Piperidine-1,4-dicarboxylic acid mono-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoro-1,1-dimethylundecyl) ester (13a). To a solution of fluorous Boc reagent 7 (6.2 g, 9.1 mmol) and triethylamine (1.01 g, 10.0 mmol) in THF was added a solution of isonipecotic acid (1.29 g, 10.0 mmol) in water. The mixture was stirred at room temperature overnight. After removal of solvent, the solid residue as stirred with chloroform (300 mL) and the white solid was filtered off. The organic solvent was evaporated and the residue was recrystallized from chloroform/hexane to give product (2.3 g). The mother liquid was concentrated and purified by column chromatography. The product (total: 5.24 g, 87%) was obtained as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 3.97 (br, 2H), 2.99 (t, J = 10.9 Hz, 2H), 2.56 - 2.48 (m, 1H), 2.18 - 1.91 (m, 6H), 1.72 - 1.59 (m, 2H), 1.51 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 180.1, 154.2, 126.1 - 106.8 (m), 80.1, 43.5, 42.8, 40.8, 31.8, 27.8, 26.2, 25.8; LRMS m/z (relative intensity)

661 (M^+, 13%), 642 (M^+ - F, 41%); HRMS calcd. for $C_{20}H_{20}NO_4F_{17}$: 661.1148, found: 661.1146,; MP: 140 - 142 °C.

2. 3-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoro-1,1-dimethyl-undecyloxycarbonylamino)propionic acid (13b). This compound was prepared by the same procedure as Example 14.1. Yield: 51%. ^1H NMR ($CDCl_3$) δ 5.08 (br, 1H), 3.42 (q, J = 5.7 Hz, 2H), 2.61 (t, J = 5.6 Hz, 2H), 2.17 - 2.04 (m, 4H), 1.49 (s, 6H); LRMS m/z (relative intensity) 622 (M^+ + H, 6%), 584 (M^+ - 2F, 32%), 562(74%), 489(51%), 133(47%), 116(100%); HRMS: found 622.0874; calcd. for $C_{17}H_{17}NO_4F_{17}$: 622.0886. MP: 94 - 95 °C.

3. 4-[(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoro-1,1-dimethyl-undecyloxycarbonylamino)-methyl]benzoic acid (13c). This compound was prepared by the same procedure as Example 14.1. Yield: 52%. ^1H NMR (MeOH-d4) δ 7.96 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 8.2 Hz, 2H), 4.30 (s, 2H), 2.20 - 2.01 (m, 4H), 1.50 (s, 6H); LRMS m/z (relative intensity) 667(M^+ - F, 59%), 547(63%), 489(54%), 196(100%), 151(55%). MP: 137 - 140 °C; HRMS: found: 66.0929; calcd. for $C_{22}H_{17}NO_3F_{17}$: 666.0937

4. (2S)-Pyrrolidine-1,2-dicarboxylic acid 1-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoro-1,1-dimethylundecyl) ester (13d). This compound was prepared by the same procedure as Example 14.1. Yield: 47%. ^1H NMR ($CDCl_3$) δ 4.37 - 4.22 (m, 1H), 3.55 - 3.35 (m, 2H), 2.26 - 1.93 (m, 8H), 1.52 - 1.47 (s, 6H); ^{13}C NMR (MeOH-d4)

δ 176.6, 155.5, 120.4 - 109.2 (m), 81.6, 60.6, 47.8, 32.8, 32.0, 31.1, 27.0, 26.5, 25.3, 24.6; LRMS m/z (relative intensity) 646 (M^+ - H, 10%), 628 (M^+ - F, 16%), 489 (56%), 114 (100%), 70 (70%); HRMS calcd. for $C_{18}H_{17}NO_2F_{17}$: 602.0974, found: 602.0988; MP: 75 - 76 °C.

5. General Procedure for the Synthesis of 15. To sixteen vials were added acids **13a-d** (0.06 mmol), amines **14a´-d´** (0.24 mmol), EDCI (0.09 mmol), HOBT (0.09 mmol) and Et_3N (0.09 mmol). Chloroform (0.5 mL) and DMF (0.5 mL) was added to each vial. These sixteen reaction mixtures were stirred at room temperature for 16 h. After concentration with a vacuum centrifuge, each reaction mixture was injected onto a preparative Fluofix™ 1EW 125 column. The column was eluted with 9:1 MeOH-H_2O for 25 min and followed by pure MeOH for 20 min. The fractions of products were collected and evaporated with a vacuum centrifuge to give the sixteen compound library **15aa´-15dd´**, which was analyzed by ^1H NMR spectroscopy. The isolated yields of the amides are listed in Figure 5.

15aa´ ^1H NMR ($CDCl_3$) δ 7.22 - 7.17 (m, 4H), 4.74 (s, 1H), 4.68 (s, 1H), 4.14 - 4.10 (m, 2H), 3.84 (s, 1H), 3.74 (t, J = 5.7 Hz, 1H), 2.95 - 2.74 (m, 4H), 2.24 - 2.05 (m, 4H), 1.74 (br, 4H), 1.51 (s, 6H).

15ab´ ^1H NMR ($CDCl_3$) δ 8.54 (d, J = 6.0 Hz, 2H), 7.16 (d, J = 5.8 Hz, 2H), 5.95 (s, 1H), 4.46 (d, J = 6.0 Hz, 2H), 4.11 (br, 2H), 2.80 (t, J = 11.8 Hz, 2H), 2.34 - 2.28 (m, 5H), 1.71 (br, 4H), 1.51 (s, 6H).

15ac ^{1}H NMR ($CDCl_3$) δ 6.08 (s, 1H), 4.08 (br, 2H), 3.53 – 3.49 (m, 1H), 3.16 – 3.11 (m, 2H), 2.81 – 2.74 (m, 3H), 2.52 (br, 1H), 2.26 – 2.03 (m, 8H), 1.85 – 1.53 (m, 7H), 1.51 (s, 6H), 1.10 (t, *J* = 7.2 Hz, 3H).

15ad ^{1}H NMR ($CDCl_3$) δ 7.56 – 7.43 (m, 4H), 5.85 (t, *J* = 5.4 Hz, 1H), 4.51 (d, *J* = 6.0 Hz, 2H), 4.10 (br, 2H), 2.79 (br, 2H), 2.36 – 2.06 (m, 5H), 1.87 – 1.60 (m, 4H), 1.51 (s, 6H).

15ba ^{1}H NMR ($CDCl_3$) δ 7.24 – 7.09 (m, 4H), 5.45 (t, *J* = 5.8 Hz, 1H), 4.74 (s, 1H), 4.59 (s, 1H), 3.83 (t, *J* = 6.0 Hz, 1H), 3.65 (t, *J* = 5.9 Hz, 1H), 3.50 – 3.45 (m, 2H), 2.92 – 2.85 (m, 2H), 2.61 – 2.58 (m, 2H), 2.22 – 1.98 (m, 4H), 1.56 (s, 6H).

15bb ^{1}H NMR ($CDCl_3$) δ 8.55 (d, *J* = 5.9 Hz, 2H), 7.17 (d, *J* = 5.8 Hz, 2H), 6.35 (s, 1H), 5.29 (s, 1H), 4.46 (d, *J* = 6.0 Hz, 2H), 3.45 (q, *J* = 6.0 Hz, 2H), 2.51 (t, *J* = 5.8 Hz, 2H), 2.11 – 1.98 (m, 4H), 1.46 (s, 6H).

15bc ^{1}H NMR ($CDCl_3$) δ 6.16 (br, 1H), 5.38 (s, 1H), 4.14 (br, 2H), 3.67 – 3.41 (m, 2H), 3.16 – 3.12 (m, 2H), 2.79 – 2.75 (m, 2H), 2.55 (br, 1H), 2.42 (br, 1H), 2.24 –2.02 (m, 4H), 1.85 – 1.68 (m, 5H), 1.48 (s, 6H), 1.08 (m, 3H).

15bd ^{1}H NMR ($CDCl_3$) δ 7.56 – 7.42 (m, 4H), 6.11 (s, 1H), 5.23 (s, 1H), 4.50 (d, *J* = 5.9 Hz, 2H), 3.48 – 3.42 (q, *J* = 6.0 Hz, 2H), 2.48 (t, *J* = 5.9 Hz, 2H), 2.22 – 1.99 (m, 4H), 1.46 (s, 6H).

15ca ^{1}H NMR ($CDCl_3$) 7.43 (d, J = 7.8 Hz, 2H), 7.33 (d, J = 7.6 Hz, 2H), 7.18 - 7.01 (m, 4H), 5.0 (br, 1H), 4.94 (br, 1H), 4.59 (br, 1H), 4.37 (m, 2H), 3.99 (br, 1H), 3.64 (br, 1H), 2.97 - 2.87 (br, 2H), 2.20 - 2.06 (m, 4H), 1.53 (s, 6H).

15cb ^{1}H NMR (CD_3OD) δ 8.47 (s, 2H), 7.85 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 8.0 Hz, 4H), 4.62 (s, 2H), 4.30 (s, 2H), 2.31 - 2.09 (m, 4H), 1.46 (s, 6H).

15cc ^{1}H NMR ($CDCl_3$) δ 7.74 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 7.9 Hz, 2H), 4.36 (s, 2H), 3.71 - 3.67 (m, 1H), 3.31 - 3.25 (m, 2H), 2.82 - 2.79 (m, 2H), 2.28 - 1.99 (m, 8H), 1.74 - 1.63 (m, 2H), 1.51 (s, 6H), 1.11 (t, J = 7.2 Hz, 3H).

15cd ^{1}H NMR ($CDCl_3$) δ 7.77 (d, J = 8.2 Hz, 2H), 7.60 - 7.41 (m, 4H), 7.34 (d, J = 7.75 Hz, 2H), 6.48 (s, 1H), 4.98 (s, 1H), 4.71 (d, J = 5.8 Hz, 2H), 4.36 (m, 2H), 2.36 - 1.91 (m, 4H), 1.51 (s, 6H).

15da ^{1}H NMR ($CDCl_3$) δ 7.26 - 7.11 (m, 4H), 4.83 - 4.58 (m, 3H), 4.10 (m, 1H), 3.70 - 3.56 (m, 3H), 2.91 - 2.84 (m, 2H), 2.24 - 1.84 (m, 8H), 1.52 (s, 6H).

15db ^{1}H NMR ($CDCl_3$), δ 8.53 (d, J = 4.3 Hz, 2H), 7.43 (s, 1H), 7.17 (d, J = 5.7 Hz, 2H), 4.51 - 4.34 (m, 3H), 3.43 - 3.36 (m, 2H), 2.40 - 1.94 (m, 8H), 1.40 (s, 6H).

15dc' ^{1}H NMR ($CDCl_3$) δ 6.91 (s, 1H), 6.42 (s, 1H), 4.29 – 4.18 (m, 1H), 3.51 – 3.40 (m, 3H), 3.13 – 2.05 (m, 2H), 2.75 (m, 1H), 2.52 (m, 1H), 2.26 – 1.68 (m, 13H), 1.52 (s, 6H), 1.08 (t, *J* = 7.2 Hz, 3H).

15dd' ^{1}H NMR ($CDCl_3$) δ 7.50 – 7.36 (m, 4H), 4.49 – 4.23 (m, 4H), 3.49 – 3.32 (m, 2H), 2.41 – 1.82 (m, 7H), 1.51 (s, 6H).

6. General Procedure for the Deprotection of 15. Amide **15** (0.05 mmol) was heated with3N HCl/MeOH (1.0 mL) at 65 °C for 16 h. The mixture was evaporated and dried under high vacuum (~1 mmHg) for 16 h. The yields of products were determined by ^{1}H NMR spectroscopy with *p*-dimethoxybenzene as an internal standard and are shown in Figure 6.

Amine from compound 15aa'. ^{1}H NMR ($CDCl_3$) δ 7.21 – 7.13 (m, 4H), 4.73 (s, 1H), 4.67 (s, 1H), 3.84 (t, *J* = 5.9 Hz, 1H), 3.75 – 3.69 (m, 1H), 3.24 (br, 2H), 2.95 – 2.78 (m, 5H), 1.79 (br, 4H).

Amine from compound 15bb'. ^{1}H NMR (CD_3OD) δ 8.98 (d, *J* = 5.9 Hz, 2H), 8.21 (d, *J* = 6.0 Hz, 2H), 4.56 (s, 2H), 3.21 (m, 2H), 2.77 – 2.73 (m, 2H).

Amine from compound 15cc'. ^{1}H NMR (CD_3OD) δ 8.01 (d, *J* = 8.1 Hz, 2H), 7.60 (d, *J* = 8.1 Hz, 2H), 4.20 (s, 2H), 3.92 – 3.58 (m, 5H), 3.30 – 3.15 (m, 2H), 2.29 – 2.02 (m, 4H), 1.41 (t, *J* = 6.9 Hz, 3H).

Amine from compound 15dd'. ^{1}H NMR (CD_3OD) δ 9.00 (s, 1H), 7.83 – 7.54 (m, 4H), 4.52 (m, 2H), 4.34 – 4.29 (m, 1H), 3.73 (s, 2H), 3.43 – 3.31 (m, 1H), 2.48 – 2.42 (m, 1H), 2.11 – 1.98 (m, 2H).

Example 15. General Procedure for the Synthesis of the Library in Figures 8 and 9. Eight vials were charged with a mixture of acid **13a** (330 mg, 0.50 mmol), an amine **17**{1-8} (2.0 mmol), EDCI (0.70 mmol), HOBT (0.70 mmol) and triethylamine (0.70 mmol) in chloroform/DMF. The reaction mixtures were stirred at room temperature overnight (16 h) and quenched with water. The organic phase was collected and evaporated with a vacuum centrifuge. These residues were charged onto eight short columns packed with fluorous reverse phase silica gel (5 g, bonded phase – $Si(Me)_2CH_2CH_2C_6F_{13}$). Each column was eluted with 80:20 MeOH-H_2O (15 mL) followed by MeOH (5 mL) and diethyl ether (20 mL). The combined MeOH and ether fractions were evaporated to dryness with a vacuum centrifuge to give library **18**{1-8}. A mixture of dichloromethane and TFA (1:1, 5 mL) was added to each of these amides **18**. The reaction mixtures were stirred at room temperature for 2.5 h. After removal of dichloromethane and TFA, stock solutions of the residues **19**{1-8} were prepared. Each of these eight solutions in DMF was added to an array of twelve halides **20**{1-12} in the presence of diisopropylethylamine (0.5 mmol). These 96 reaction mixtures were heated at 50 °C for 48 h. After concentration, the mixtures were purified with a PrepLCMS system. In 89 out of 96 reactions, the desired products were detected by LC-MS and isolated in yields from 5 to

100% (Figure 9). Spectroscopic data for twelve members of library **21**{1-8, 1-12} are listed below.

Compound 21{*2,2*}. ^{1}H NMR (DMSO-d6) δ 9.3 (br, 2H), 8.04 (t, *J* = 3.3 Hz, 1H), 7.28 (m, 2H), 7.20 (m, 2H), 6.76 (m, 2H), 6.01 (m, 2H), 3.94 (t, *J* = 4.1 Hz, 2H), 3.47 (d, *J* = 7.1 Hz, 2H), 3.28 (q, *J* = 4.0 Hz, 2H), 2.97 – 2.84 (m, 4H), 2.70 (t, *J* = 4.3 Hz, 2H), 2.32 – 2.29 (m, 1H), 2.11 – 2.05 (m, 2H), 1.84 – 1.71 (m, 4H); ^{13}C NMR (DMSO-d6) δ 172.5, 139.4, 128.6, 128.2, 126.1, 120.5, 107.9, 53.6, 51.2, 45.8, 35.0, 25.9, 25.5.

Compound 21{*3,7*}. ^{1}H NMR (DMSO-d6) δ 9.21 (br, 1H), 8.50 (t, *J* = 5 Hz, 2H), 7. 32 (t, *J* = 4.5 Hz, 2H), 7.24 (t, *J* = 4.5 Hz, 2H), 5.82 – 5.77 (m, 1H), 5.03 (d, *J* = 10.5 Hz, 1H), 4.98 (d, *J* = 6.1 Hz, 1H), 4.26 (d, *J* = 3.5 Hz, 2H), 3.51 (d, *J* = 7.1 Hz, 2H), 3.05 – 3.01 (m, 2H), 2.89 (q, *J* = 6.6 Hz, 2H), 2.47 – 2.44 (m, 1H), 2.05 (q, *J* = 4.3 Hz, 2H) 1.93 (d, *J* = 8.1 Hz, 2H), 1.84 – 1.79 (m, 2H), 1.67 – 1.60 (m, 2H), 1.37 (q, *J* = 4.5 Hz, 2H); ^{13}C NMR (DMSO-d6) δ 172.7, 139.4, 138.0, 128.3, 127.1, 126.8, 115.3, 55.8, 51.1, 41.9, 32.5, 25.9, 25.2, 22.7.

Compound 21{*2,9*} ^{1}H NMR (DMSO-d6) δ 8.03 (s, 1H), 7.30 – 7.27 (m, 2H), 7.21 – 7.18 (m, 2H), 6.94 – 6.89 (m, 5H), 4.7 (s, 1H), 4.29 (dd, *J* = 7.0, 1.1 Hz, 1H), 3.05 (s, 2H), 2.71 (t, *J* = 4.4 Hz, 2H), 2,35 (s, 1H), 1.89 (m, 4H); ^{13}C NMR (DMSO-d6) δ 172.5, 139.4, 128.7, 128.3, 126.1, 121.8, 117.4, 117.2, 68.0, 65.0, 55.8, 52.4, 51.7, 35.0, 25.9.

Compound 21{*4,4*} ^{1}H NMR (DMSO-d6) δ 9.47 (s, 1H), 8.01 (t, *J* = 3.3 Hz, 1H), 7.37 – 7.34 (m, 2H), 7.30 – 7.25 (m, 2H), 7.10 (d, *J* = 5.0 Hz, 2H), 6.84 (d, *J* = 5.0 Hz, 2H), 3.72 (s, 3H), 3.57 (m, 2H), 3.34 – 3.31 (m, 5H), 3.00 – 2.84 (m, 4H), 2.64 (t, *J* = 4.4 Hz, 2H), 2.37 – 2.32 (m, 1H), 1.89 – 1.73 (m, 3H); ^{13}C NMR (DMSO-d6) δ 172.5, 157.7, 136.9, 131.2, 129.7, 128.8, 126.9, 114.1, 113.7, 56.6, 55.1, 51.2, 34.2, 29.5, 25.9.

Compound 21{*1,1*}. ^{1}H NMR (DMSO-d6) δ 8.41 (t, *J* = 3.5 Hz, 1H), 7.15 (d, *J* = 5.1 Hz, 2H), 6.88 (d, *J* = 5.1 Hz, 2H), 4.25 – 4.19 (m, 6H), 3.72 (s, 3H), 3.01 (s, 2H), 1.92 (br, 4H), 1.24 (t, *J* = 4.2 Hz, 3H); ^{13}C NMR (DMSO-d6) δ 172.5, 165.9, 158.2, 131.3, 128.5, 113.7, 61.9, 55.1, 41.4, 25.6, 13.9.

Compound 21{*6,10*}. ^{1}H NMR (DMSO-d6) δ 8.54 (t, *J* = 3.5 Hz, 1H), 7.78 – 7.72 (m, 2H), 7.69 – 7.57 (m, 4H), 7.50 – 7.44 (m, 3H), 7.37 – 7.31 (m, 3H), 4.31 – 4.25 (m, 4H), 3.41 (d, *J* = 7.1 Hz, 2H), 2.99 – 2.95 (m, 2H), 2.50 – 2.47 (m, 1H), 1.97 – 1.80 (m, 4H); ^{13}C NMR (DMSO-d6) δ 172.7, 139.9, 138.8, 138.6, 133.3, 132.5, 129.0, 127.8, 126.9, 126.6, 57.7, 50.9, 41.7, 25.8.

Compound 21{*5,3*}. ^{1}H NMR (DMSO-d6) δ 11.0 (s, 1H), 10.2 (s, 1H), 7.62 – 7.57 (m, 3H), 7.51 (d, *J* = 4.5 Hz, 2H), 7.38 (d, *J* = 4.8 Hz, 2H), 7.25 (s, 1H), 7.12 – 7.09 (m, 1H), 7.04 – 7.01 (m, 1H), 3.72 (d, *J* = 7.1 Hz, 2H), 3.14 – 3.11 (m, 2H), 3.03 (q, *J* = 6.7 Hz, 2H), 2.66 – 2.60 (m, 1H), 2.09 – 186

(m, 4H); ^{13}C NMR (DMSO-d6) δ 171.9, 138.4, 136.3, 131.5, 126.6, 123.2, 121.3, 121.1, 118.5, 118.2, 114.9, 111.6, 108.9, 56.1, 51.0, 25.8, 19.8.

Compound 21{*8,12*}. ^{1}H NMR (DMSO-d6) δ 8.05 (s, 1H), 7.87 (d, *J* = 4.5 Hz, 2H), 7.63 (d, *J* = 4.5 Hz, 2H), 7.57 (d, *J* = 4.2 Hz, 2H), 7.47 – 7.42 (m, 3H), 7.36 – 7.33 (m, 1H), 7.27 (d, *J* = 4.7 Hz, 2H), 4.98 (s, 4H), 3.52 – 3.49 (m, 2H), 3.02 – 3.00 (m, 2H), 2.76 (t, *J* = 4.3 Hz, 2H), 2.39 (s, 3H), 1.90 (br, 4H).

Compound 21{*5,11*}. ^{1}H NMR (DMSO-d6) δ 9.2 (s, 1H), 8.04 (d, *J* = 4.5 Hz, 1H), 7.30 (s, 1H), 7.26 (d, *J* = 5.7 Hz, 1H), 7.02 (d, *J* = 5.0 Hz, 1H), 3.93 (s, 1H), 3.51 (d, *J* = 7.2 Hz, 2H), 3.06 – 3.02 (m, 2H), 2.93 – 2.78 (m, 4H), 2.56 – 2.53 (m, 2H), 2.38 – 2.35 (m, 1H), 1.88 – 1.76 (m, 5H), 1.64 – 1.50 (m, 3H), 0.90 (d, *J* = 4.6 Hz, 6H); ^{13}C NMR (DMSO-d6) δ 172.3, 138.4, 134.1, 131.2, 130.9, 128.4, 118.6, 54.5, 51.1, 44.3, 34.3, 31.9, 27.9, 26.9, 26.0, 25.9, 25.7, 22.1.

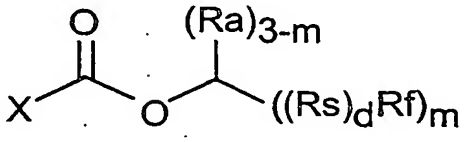
Compound 21{*5,5*}. ^{1}H NMR (DMSO-d6) δ 8.04 (d, *J* = 4.5 Hz, 1H), 7.35 – 7.26 (m, 4H), 7.04 – 6.99 (m, 4H), 4.33 (t, *J* = 2.8 Hz, 2H), 3.94 – 3.92 (m, 1H), 3.61 (d, *J* = 7.2 Hz, 2H), 3.57 (s, 2H), 3.04 – 3.02 (m, 2H), 2.94 – 2.89 (m, 1H), 2.87 – 2.78 (m, 2H), 2.56 – 2.53 (m, 1H), 2.40 – 2.37 (m, 1H), 1.90 – 1.84 (m, 4H), 1.64 – 1.62 (m, 1H); ^{13}C NMR (DMSO-d6) δ 172.3, 157.5, 138.4, 134.1, 131.2, 130.9, 129.6, 128.4, 121.4, 118.6, 114.7, 62.0, 55.0, 51.8, 44.3, 34.3, 27.9, 26.9, 25.9.

Compound 21{*1,8*}. ^{1}H NMR (DMSO-d6) δ 8.42 (t, *J* = 3.4 Hz, 1H), 7.15 (d, *J* = 5.1 Hz, 2H), 6.87 (d, *J* = 5.2 Hz, 2H), 4.19 (d, *J* = 3.3 Hz, 2H), 3.72 (s, 3H), 2.94 (t, *J* = 6.9 Hz, 2.84 (t, *J* = 4.5 Hz, 1H), 2.74 (t, *J* = 4.5 Hz, 1H), 2.4 (m, 1H), 1.93 – 1.77 (m, 4H); ^{13}C NMR (DMSO-d6) δ 171.6, 170.6, 169.5, 130.3, 127.5, 112.7, 54.1, 50.9, 50.4, 40.4, 27.7, 27.4, 25.0.

Although the present invention has been described in detail in connection with the above examples, it is to be understood that such detail is solely for that purpose and that variations can be made by those skilled in the art without departing from the spirit of the invention except as it may be limited by the following claims.

WHAT IS CLAIMED IS:

1. A method of increasing the fluorous nature of a compound, including the step of reacting the compound with at least one second compound having the formula:



wherein Rf is a fluorous group, Rs is a spacer group, d is 1 or 0, m is 1, 2 or 3, Ra is an alkyl group and X is a leaving group.

2. The method of Claim 1 wherein the leaving group is a halide, $-N_3$, -CN, RO-, NH_2O-, NHRO-, NR_2O-, RCO_2-, $ROCO_2$-, $RNCO_2$-, RS-, RC(S)O-, RCS_2-, RSC(O)S-, $RSCS_2$- $RSCO_2$-, ROC(S)O-, $ROCS_2$-, RSO_2-, RSO_3-, $ROSO_2$-, $ROSO_3$-, RPO_3-, $ROPO_3$-, an N-imidazolyl group, an N-triazolyl group, an N-benzotriazolyl group, a benzotriazolyloxy group, an imidazolyloxy group, an N-imidazolinone group, an N-imidazolone group, an N-imidazolinethione group, an N-succinimidyl group, an N-phthalimidyl group, an N-succinimidyloxy group, an N-phthalimidyloxy group, -ON=C(CN)R, or a 2-pyridyloxy group, wherein R is an alkyl group or an aryl group.

3. The method of Claim 1 wherein Rs is an alkylene group.

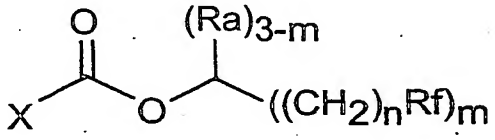
4. The method of Claim 4 wherein Rs is $-CH_2CH_2-$.

5. The method of Claim 1 wherein Ra is a C_1-C_6 alkyl group.

6. The method of Claim 1 wherein the fluorous group is a perfluorocarbon, a fluorohydrocarbon, a fluorinated ether or a fluorinated amine.

7. The method of Claim 1 wherein fluorous group is a perfluoroalkyl group.

8. A compound having the formula:



wherein Rf is a fluorous group, n is an integer between 0 and 6, m is 1, 2 or 3, Ra is an alkyl group and X is a leaving group.

9. The compound of Claim 8 wherein the leaving groups is a halide, $-N_3$, -CN, RO-, NH_2O-, NHRO-, NR_2O-, RCO_2-, $ROCO_2$-, $RNCO_2$-, RS-, RC(S)O-, RCS_2-, RSC(O)S-, $RSCS_2$-, $RSCO_2$-, ROC(S)O-, $ROCS_2$-, RSO_2-, RSO_3-, $ROSO_2$-, $ROSO_3$-, RPO_3-, $ROPO_3$-, an N-imidazolyl group, an N-triazolyl group, an N-benzotriazolyl group, a benzotriazolyloxy group, an imidazolyloxy group, an N-imidazolinone group, an N-imidazolone group, an N-imidazolinethione group, an

N-succinimidyl group, an N-phthalimidyl group, an N-succinimidyloxy group, an N-phthalimidyloxy group, -ON=C(CN)R, or a 2-pyridyloxy group, wherein R is an alkyl group or an aryl group.

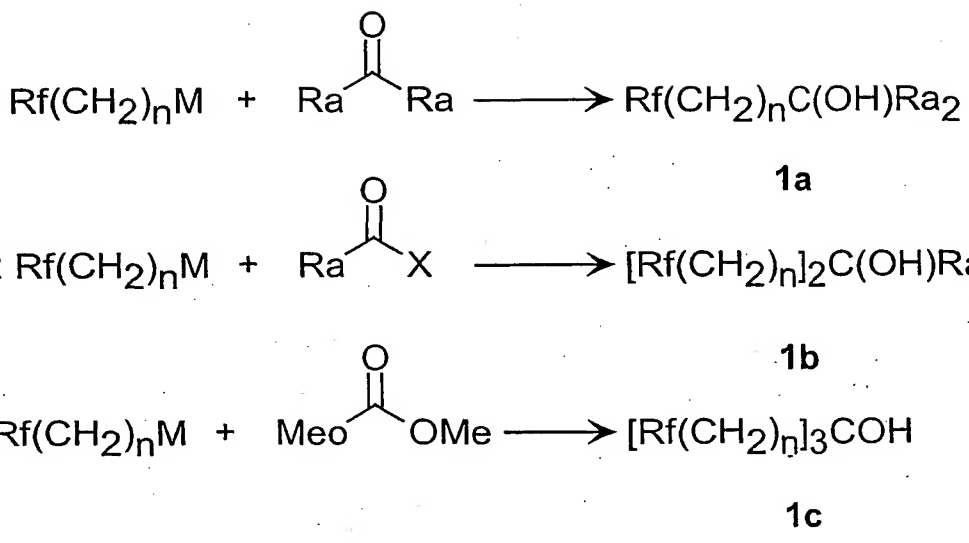
10. The compound of Claim 9 wherein Ra is a C_1-C_6 alkyl group.

11. The compound of Claim 8 wherein the fluorous group is a perfluorocarbon, a fluorohydrocarbon, a fluorinated ethers or a fluorinated amine.

12. The compound of Claim 11 wherein fluorous group is a perfluoroalkyl group.

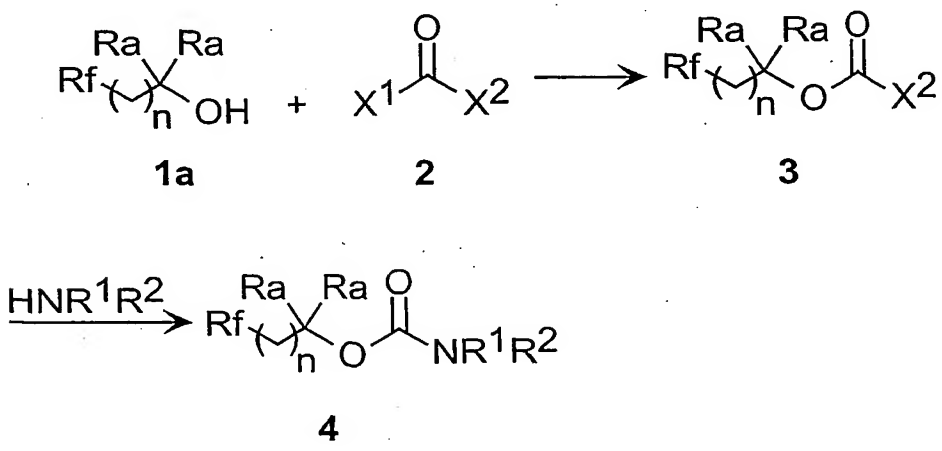
13. The compound of Claim 8 wherein X is Cl, N_3 or -ON=C(CN)Ph.

Preparations of alcohols



M = Mg or Li; X = Cl or OR'; n = 2 or 3; Rf = C_nF_{2n+1}

Preparations of Boc reagents and reaction with amines



Fluorous Boc protected derivatives

Figure 1

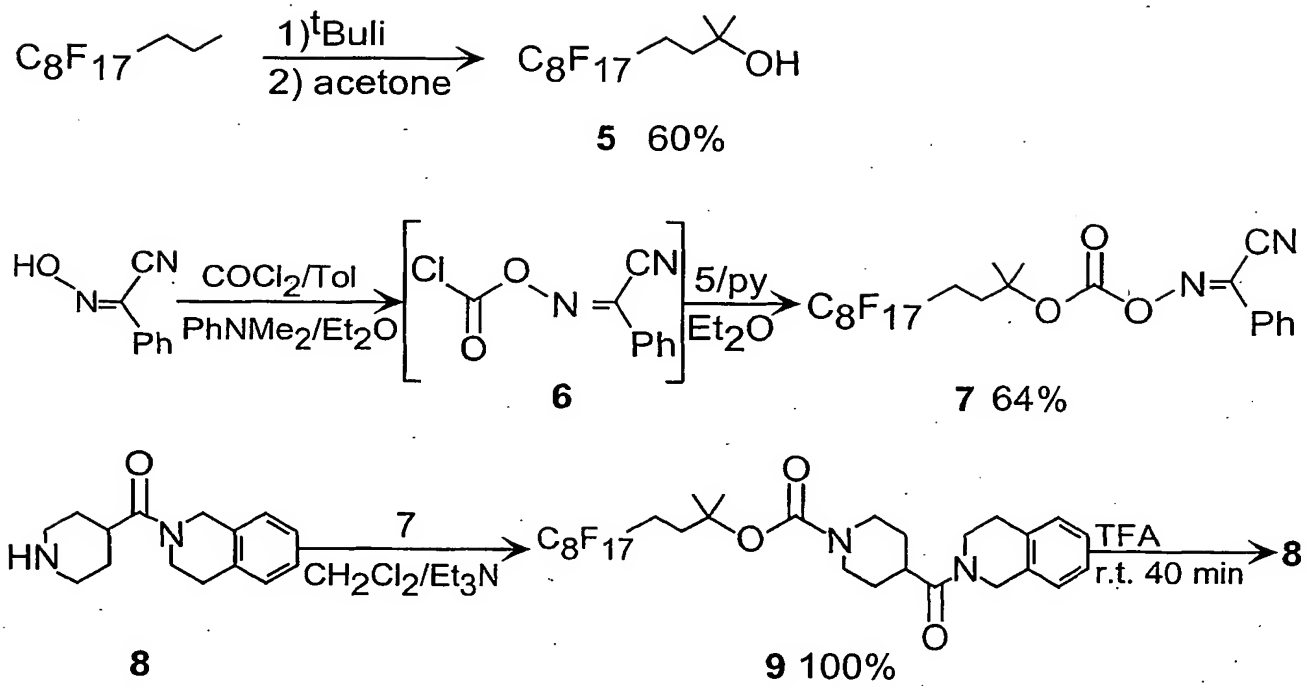


Figure 2

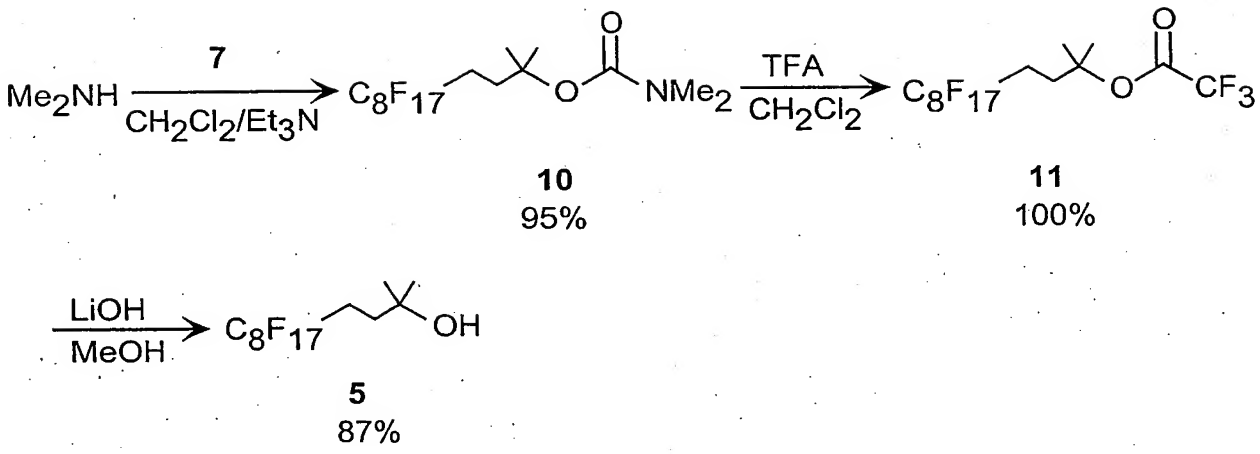
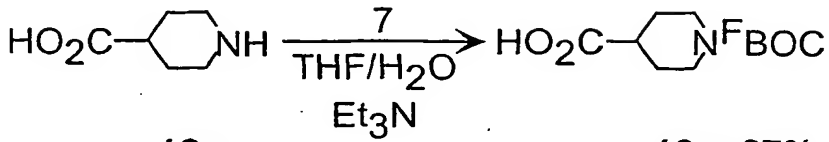


Figure 3

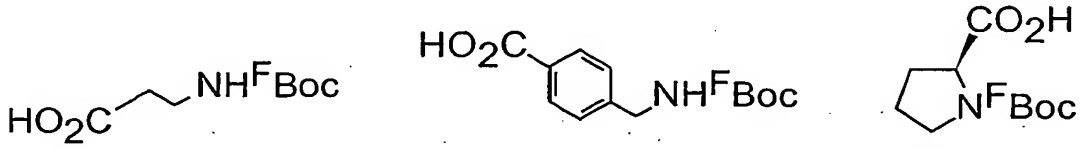
Examples of ^{F}Boc protection

^{F}BOC = C_8F_{17}



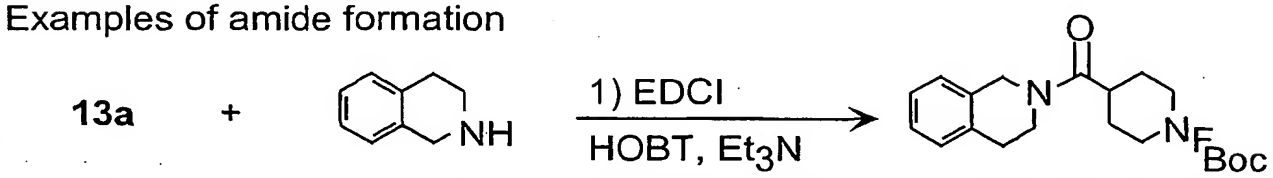
12a **13a** 87%

Similarly prepared from the corresponding amino acids **12b-c**



13b 51% **13c** 52% **13d** 47%

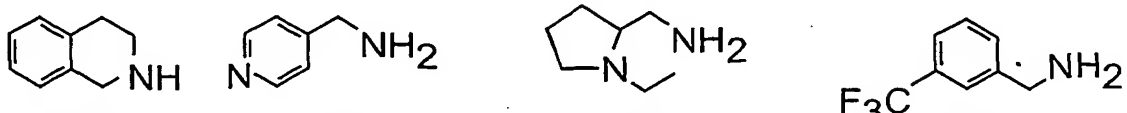
Examples of amide formation



1 equiv 3 equiv **15aa'** (same as **9**)

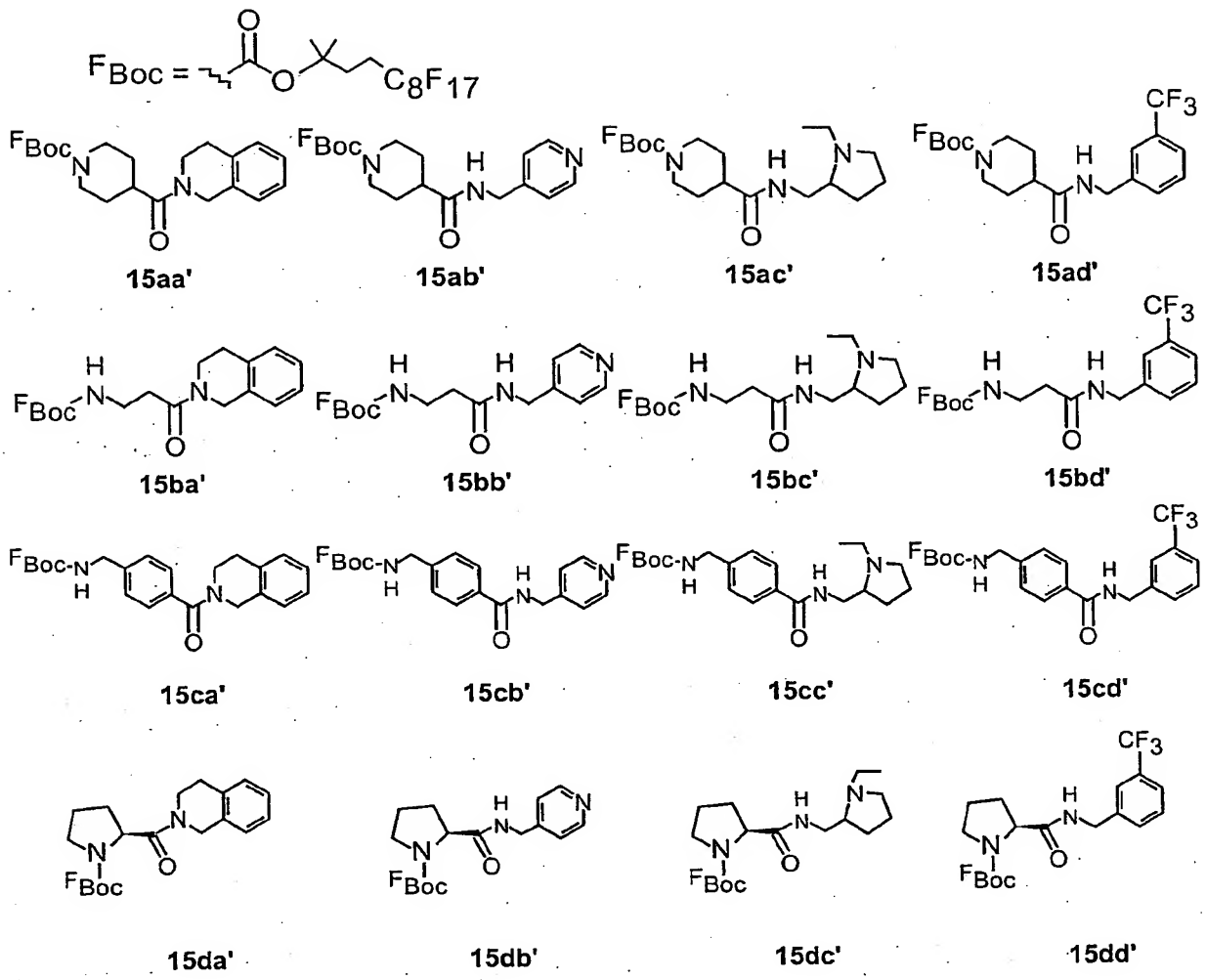
4 acids **13a-d** 4 amines **14a'-d'** 16 amines **15aa'-dd'**

Structures of amines **14a'-d'**



14a' **14b'** **14c'** **14d'**

Figure 4

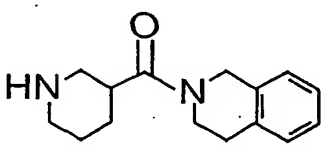


Yields of products **15**

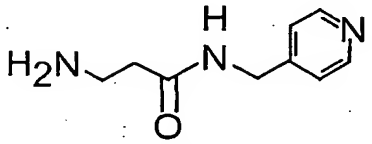
14 \ 13	a	b	c	d
a'	71	82	21	quan.
b'	44	98	88	81
c'	37	23	94	59
d'	31	77	73	87

Figure 5

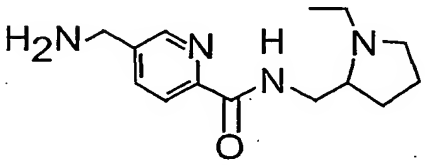
Products generated by deprotection of the fluorous Boc protected amides with HCl/MeOH



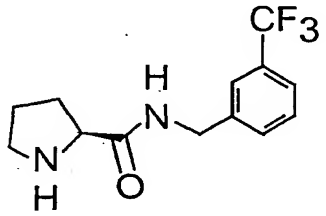
from **53aa'** 92%



from **15bb'** 100%



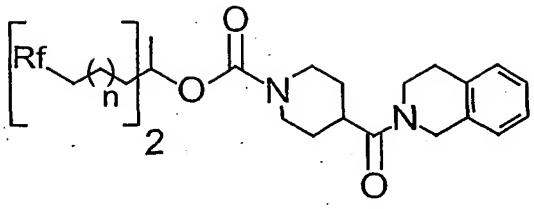
from **15cc'** 53%



from **15dd'** 86%

Yields determined by 1H NMR spectroscopy with the corresponding hydrochloride salts.

Figure 6



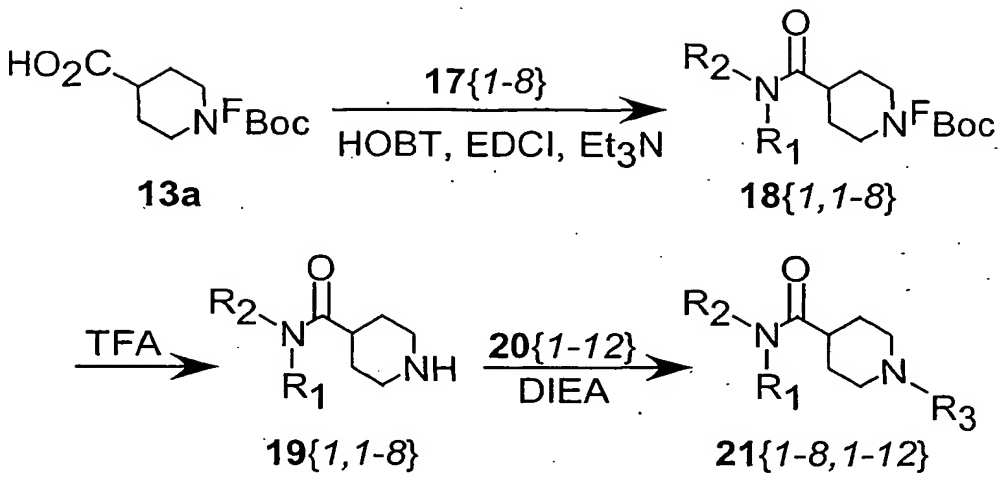
	Rf	n
16a	C_6F_{13}	0
16b	C_6F_{13}	1
16c	C_4F_9	1

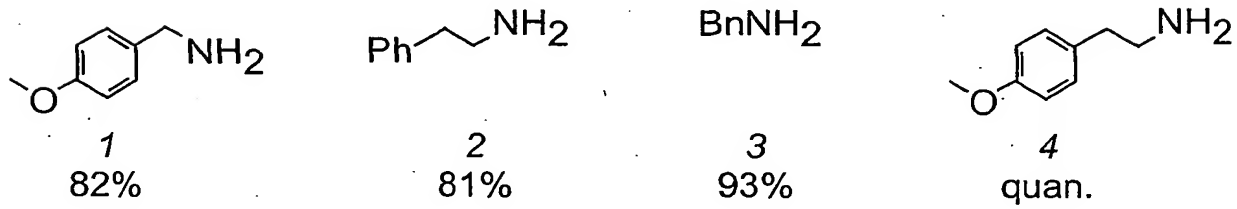
HPLC retention times on a Fluofix column

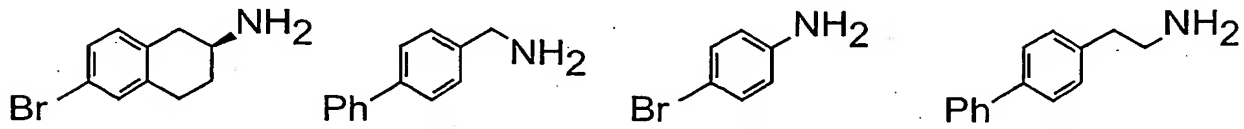
Compound	retention time (min)[a)]
9	22.5
16a	33.8
16b	33.4
16c	24.1

a) HPLC method: MeOH:H_2O (4:1), 30 min gradient to 100% MeOH, 10 min gradient to MeOH:THF (9:1)

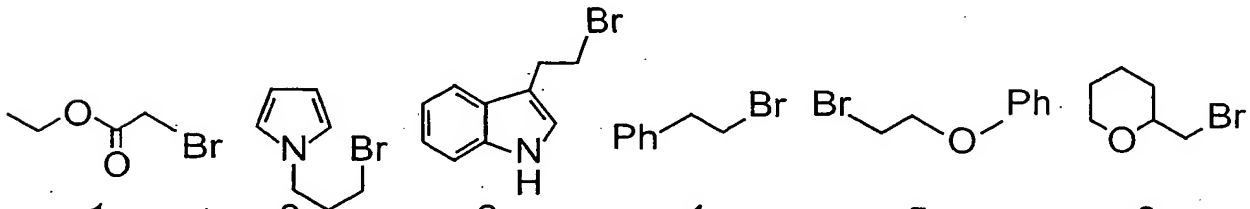
Figure 7

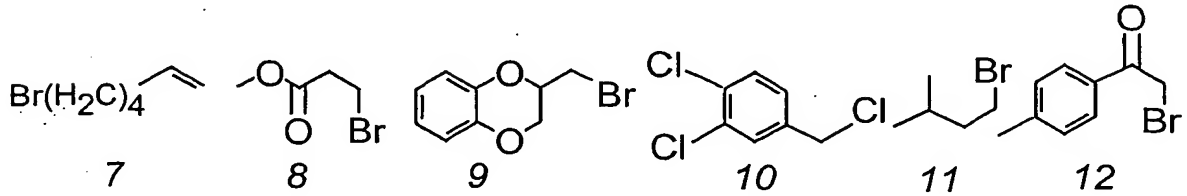






Diversity reagents 17{*1-8*}





Diversity reagents 20{*1-12*}

Figure 8

	19{1}	**19**{2}	**19**{3}	**19**{4}	**19**{5}	**19**{6}	**19**{7}	**19**{8}
20{1}	(70)	quan.	94	quan.	89	95	5	60
20{2}	71	(80)	84	80	61	70	48	48
20{3}	48	58	0	65	10	41	(30)	28
20{4}	(46)	62	85	(50)	50	43	36	32
20{5}	56	72	68	52	(48)	47	41	41
20{6}	12	9	10	10	0	9	0	(9)
20{7}	51	63	(71)	54	51	60	0	36
20{8}	72	82	83	94	81	82	5	56
20{9}	13	(18)	17	10	0	14	0	11
20{10}	61	77	68	81	52	(71)	11	40
20{11}	49	63	62	49	(44)	45	5	32
20{12}	27	38	31	32	0	25	14	(14)

All compounds were characterized by LCMS. Compound with yields in parentheses were also characterized by proton NMR spectroscopy

Figure 9

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(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
- *with international search report*
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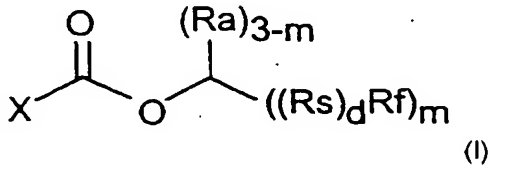
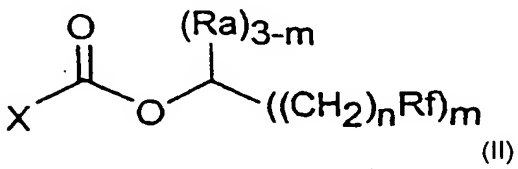
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: FLUOROUS TAGGING COMPOUNDS AND THEIR USE



(I)



(II)

(57) Abstract: A method of increasing the fluorous nature of a compound includes the step of reacting the compound with at least one second compound having formula (I) wherein Rf is a fluorous group, Rs is a spacer group, d is 1 or 0, m is 1, 2 or 3, Ra is an alkyl group and X is a suitable leaving group. A compound has formula (II) wherein Rf is a fluorous group, n is an integer between 0 and 6, m is 1, 2 or 3, Ra is an alkyl group and X is a leaving group.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/14350

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C269/04 C07C255/33 C07C281/00 C07C69/96 C07B61/00
C07D401/06 C07D401/12 C07D211/60 C07D207/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07B C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 732 274 A (FOX W ET AL) 8 May 1973 (1973-05-08) examples 2,8 claim 1 ---	8-13
X	GB 1 149 280 A (ICI LTD) 23 April 1969 (1969-04-23) (C2F5)3COC(O)Cl example 2 ---	8,9, 11-13
X	US 3 627 799 A (ANDERSON LOWELL R ET AL) 14 December 1971 (1971-12-14) (CF3)3COC(O)Cl example 6 --- -/--	8,9, 11-13

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 January 2002	19/02/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Diederen, J

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/14350

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; BASKAKOV Y.A ET AL: "Preparation of N-(hydroxyalkyl)- and N-'(aminocarbonyloxy)alkyl)!carbamates as stress-reducing plant growth regulators. " retrieved from Database accession no. 1991:558738 XP002186516 Compounds with RN 136205-26-0, 136205-25-9 abstract -& WO 91 07381 A (VNII KHIM ET AL) 30 May 1991 (1991-05-30) ---	8-13
A	HUDLICKY M: "NEW SYNTHESIS AND REACTIONS OF PERFLUORO-TERT-BUTYL CHLOROFORMATE" JOURNAL OF FLUORINE CHEMISTRY, ELSEVIER SEQUOIA, LAUSANNE, CH, vol. 20, 1982, pages 649-658, XP001011888 ISSN: 0022-1139	1
X	abstract Experimental, Carbamates IIIe and IIIf from I ---	8,9, 11-13
A	CURRAN, D.P.; LUO, Z.: "Fluorous Synthesis with FEwer Fluorines (Light Fluorous Synthesis): Separation of Tagged from Untagged Products by Solid-Phase Extraction with Fluorous Reverse-Phase Silica Gel" J. AM. CHEM. SOC., vol. 121, 1999, pages 9069-72, XP002186512 abstract Amides 1a-i (prepared via standard acylation reaction with the corresponding acid chloride, see supporting information S4) page 9070, left-hand column -right-hand column ---	1,8
A	STUDER, A ET AL.: "Fluorous Synthesis: A fFluorous-Phase Strategy for Improving Separation Efficiency in Organic Synthesis" SCIENCE, vol. 275, 1997, pages 823-6, XP002186513 abstract The use of fluorinated silyl protecting group and extraction in FC-72 (mixture fluorinated hexanes) figure 2 -----	1,8

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-12 (partially)

Present claims 1-12 relate to an extremely large number of possible compounds and methods. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds and methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds and methods in which X, as defined in claims 1 and 8, is Cl, N3 or -ON=C(CN)Ph (see claim 13).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 01/14350

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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GB 1149280 A	23-04-1969	NONE	
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WO 9107381 A	30-05-1991	WO 9107381 A1	30-05-1991
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		GB 2245566 A	08-01-1992